Drug-eluting stents compared to bare-metal stents improve mortality in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention - A Nationwide Prospective Analysis of AMIS

Jaguszewski, Milosz ; Radovanovic, Dragana ; Nallamothu, Brahmajee K ; Urban, Philip ; Erne, Paul

Abstract: BACKGROUND: Recently, it has been suggested that the type of stent used in primary percutaneous coronary interventions (pPCI) might impact on outcomes of patients with acute myocardial infarction (AMI). Indeed, drug-eluting stents (DES) reduce neointimal hyperplasia when compared to bare-metal stents (BMS); moreover the later generation DES due to its biocompatible polymer coatings and stent design allow for greater deliverability, improved endothelial healing and therefore less restenosis rate and thrombus generation. However, data on the safety and performance of DES in large cohorts of AMI are still limited. AIM: To compare the early outcome of DES vs. BMS in acute myocardial infarction patients. METHODS: This was a prospective, multicenter analysis containing patients from 64 hospitals in Switzerland with AMI undergoing pPCI between 2005 and 2013. The primary endpoint was in-hospital all-cause death, whereas the secondary endpoint included a composite measure of major adverse cardiac and cerebrovascular events (MACCE) of death, reinfarction, and cerebrovascular event. RESULTS: Of 20 464 patients with the primary diagnosis of AMI and enrolled to the AMIS Plus Registry, 15 026 were referred for pPCI and 13 442 received stent implantation. 10 094 patients were implanted with DES and 2 260 with BMS. The overall in-hospital mortality was significantly lower in patients with DES as compared to those with BMS implantation (2.6% vs. 7.1%, p<0.001). The overall in-hospital MACCE after DES was similarly lower when compared with BMS (3.5% vs. 7.6%; p<0.001). After adjusting for all confounding covariables, the DES remained an independent predictor for lower in-hospital mortality (odds ratio [OR], 0.51;95% confidence interval [CI], 0.40 to0.67; p<0.001). Since groups differed as regards baseline characteristics and pharmacological treatment we performed a propensity score matching (PSM) to limit potential biases. Similarly, after the PSM, DES implantation remained independently associated with reduced risk of in-hospital mortality (adjusted odds ratio [aOR], 0.54; 95% confidence interval [CI], 0.39 to 0.76; p<0.001). Conclusion: In unselected patients from a nationwide, real-world cohort, we found DES as compared to BMS was associated with lower in-hospital mortality and MACCE. The identification of optimal treatment strategies of patients with AMI needs further randomized evaluation; however, our findings suggest potential benefit with DES.

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Drug-eluting stents compared to bare-metal stents improve short-term survival in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: A Nationwide Prospective Analysis of AMIS (Acute Myocardial Infarction in Switzerland) Plus Registry

Stenty uwalniające leki poprawiają rokowanie u pacjentów z ostrym zawałem serca poddanych pierwotnej przezskórnej rewaskularyzacji

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Abstract

Background: Recently, it has been suggested that the type of stent used in primary percutaneous coronary interventions (pPCI) might impact on outcomes of patients with acute myocardial infarction (AMI). Indeed, drug-eluting stents (DES) reduce neointimal hyperplasia when compared to bare-metal stents (BMS); moreover the later generation DES due to its biocompatible polymer coatings and stent design allow for greater deliverability, improved endothelial healing and therefore less restenosis rate and thrombus generation. However, data on the safety and performance of DES in large cohorts of AMI are still limited.

Aim: To compare the early outcome of DES vs. BMS in acute myocardial infarction patients.

Methods: This was a prospective, multicenter analysis containing patients from 64 hospitals in Switzerland with AMI undergoing pPCI between 2005 and 2013. The primary endpoint was in-hospital all-cause death, whereas the secondary endpoint included a composite

measure of major adverse cardiac and cerebrovascular events (MACCE) of death, reinfarction, and cerebrovascular event.

Results: Of 20 464 patients with the primary diagnosis of AMI and enrolled to the AMIS Plus Registry, 15 026 were referred for pPCI and 13 442 received stent implantation. 10 094 patients were implanted with DES and 2 260 with BMS. The overall in-hospital mortality was significantly lower in patients with DES as compared to those with BMS implantation (2.6% vs. 7.1%, p<0.001). The overall in-hospital MACCE after DES was similarly lower when compared with BMS (3.5% vs. 7.6%; p<0.001). After adjusting for all confounding covariables, the DES remained an independent predictor for lower in-hospital mortality (odds ratio [OR], 0.51;95% confidence interval [CI], 0.40 to0.67; p<0.001). Since groups differed as regards baseline characteristics and pharmacological treatment we performed a propensity score matching (PSM) to limit potential biases. Similarly, after the PSM, DES implantation remained independently associated with reduced risk of in-hospital mortality (adjusted odds ratio [aOR], 0.54; 95% confidence interval [CI], 0.39 to 0.76; p<0.001).

Conclusion: In unselected patients from a nationwide, real-world cohort, we found DES as compared to BMS was associated with lower in-hospital mortality and MACCE. The identification of optimal treatment strategies of patients with AMI needs further randomized evaluation; however, our findings suggest potential benefit with DES.

Key words: acute myocardial infarction, drug-eluting stents, bare-metal stents

Introduction

Primary percutaneous coronary intervention (pPCI) with stent implantation has been acknowledged as the most optimal treatment strategy in patients with acute myocardial infarction (AMI)[1]. pPCI with bare metal stent (BMS) implantation has been associated with a significant improvement in clinical outcome and therefore has become a standard of practice[1]. The introduction of drug eluting stents (DES) has emerged as a rational pPCI alternative in this particular setting of AMI[2].

Recently, it has been suggested that the type of stent used in pPCI might impact on outcomes of patients with AMI[3]. Indeed, DES was affirmed to reduce neointimal hyperplasia and persistent fibrin deposition when compared to BMS[4]; moreover the later generation DES due to its biocompatible polymer coatings and stent design allow for greater deliverability, improved endothelial healing and therefore less restenosis rate and reinfarction[5]; however, concerns have been raised with regard to the safety of DES, particularly in the AMI setting[5-7].

In recently published COMFORTABLE AMI Trial the comparison of new-generation biolimus-eluting stents (BES) and BMS resulted in reduction of a composite of major adverse cardiovascular events among patients with STEMI undergoing pPCI[8]. However, the randomized clinical trials (RCTs) did not confirm the benefit of DES as regards the mortality rate[9]. Due to the conflicting reports regarding the hard outcomes after DES versus BMS implantation, the most accurate treatment strategy of pPCI during AMI remains nowadays still the matter of debate.

In this context, we performed a post hoc analysis from the prospective, multicenter cohort to investigate whether DES as compared to BMS influence early outcome in the setting of AMI. The presented all-comer observation addresses the real-world setting and therefore reflects the care of patients in routine clinical practice.

Methods

Study design and population

The AMIS (Acute Myocardial Infarction in Switzerland) Plus project was founded in January 1997 as a large, nationwide prospective registry of patients admitted with acute coronary syndrome (ACS) to 82 hospitals in Switzerland, including ST-segment-elevation myocardial infarction (STEMI), non- ST-segment-elevation myocardial infarction (NSTEMI) and unstable angina (UA) (Figure 1). The registry is officially supported by the Swiss Societies of Cardiology, Internal Medicine and Intensive Care Medicine. The design of the registry has been previously described[10, 11]. All participating centers, ranging from community institutions to large tertiary facilities, provide blinded data, being subsequently centralized at the AMIS Plus Data Center. All data provided through an internet- or paper-based questionnaires, are subsequently checked for plausibility and consistency in the Institute of Social and Preventive Medicine at the University of Zurich, Switzerland. The registry was approved by the Over-Regional Ethics Committee for Clinical Studies, the Swiss Board for Data Security and all cantonal Ethic Commissions.

Data extraction

The AMIS Plus Central Database collects 230 items including medical history, co-morbidities, known cardiovascular risk factors (dyslipidemia, arterial hypertension, diabetes, obesity and smoking), clinical presentation, out-of-hospital management, early in-hospital management, reperfusion therapy, hospital course, diagnostic tests used or planned, length of stay, discharge medication and discharge destination, immediate drug treatment and discharge medication.

The non-cardiovascular co-morbidities were assessed using the Charlson Index[12]. Patients are enrolled in the registry based on their final diagnosis.

Patients selection

Between January 2005 and March 2013, 20 464 patients with AMI (STEMI and NSTEMI) were enrolled to the AMIS Plus Registry, 17 651 underwent any pPCI. Of those, 15 026 underwent pPCI and 13 442 pPCI with stent implantation. 10 094 patients were implanted with DES and 2 260 with BMS. 942 patients were excluded from the final analysis due to lacking data regarding the stent type. 146 patients received variable absorbable scaffolds. The study flow chart is presented on Figure 2.

Definitions

The STEMI was defined by characteristic symptoms with ECG changes and cardiac marker elevation (creatine kinase MB fraction at least twice the upper limit of normal or troponin I or T above individual hospital cut-off levels for MI). All patients required ST-segment elevation and/or the new development of left bundle branch block on the initial ECG at presentation. NSTEMI was defined as cardiac marker elevation with no ST-elevation in admission ECG.

Reinfarction was defined as clinical signs or symptoms of ischemia with ECG changes indicative of new ischemia (new ST-changes or new LBBB) and a re-rise of biomarkers following the initial infarction. A cerebrovascular event was defined as any event due to ischemic, thrombotic or hemorrhagic disturbances confirmed by a neurologist or imaging modality.

Multivessel disease (MVD) was defined as a presence of angiographic stenosis of ≥50% in at least 2 main epicardial coronary arteries and/or involving the left main (LM) when a surgical bypass graft was concern. The decision regarding single-vessel PCI (S-PCI) or multivessel PCI (M-PCI) attempt and DES or BMS implantation was performed at the physician’s discretion.

Study endpoints

The primary endpoint of the study was in-hospital all-cause mortality. Secondary endpoint include a composite endpoint of MACCE (major adverse cardiac and cerebrovascular events) including death, reinfarction and/or cerebrovascular event.

Statistical analysis

The results are presented as percentages for categorical variables and analyzed using the non-parametric Pearson $\chi 2$ test or Fisher's exact test as appropriate. Continuous variables are expressed as means ± standard deviation (SD) and compared using the Student's unpaired t-test for normal distribution and continuous non-normally distributed variables are expressed as median and interquartile ranges and analyzed using the Mann-Whitney U test. To examine predictors for in-hospital mortality the multivariate logistic regression was used and included the following variables: stent type (BMS or DES), multi-vessel revascularization, age, gender, LM involvement, Killip class>2, Charlson comorbidities weighted index >2 and out-of-hospital resuscitation. To limit the observational character of the study we performed a propensity score matching to create matched DES (n=2137) and BMS (n=2137) cohorts. Optimal matching was obtained using a logistic regression model with stent type used as dependent variable. Independent variables were age, gender, resuscitation before admission, STEMI, Killip class >2, Charlson comorbidity score ≥2 and MVD.
All statistical tests were 2-tailed. P-value of < 0.05 was considered statistical significant. SPSS software (version 19, SPSS Inc, Chicago, Illinois, USA) was used for all statistical analyses.

Results

Study population and baseline

Of the included 12 354 patients undergoing the pPCI and stent implantation during AMI between 2005 and 2013, we identified 10 094 patients (82%) with DES and 2 260 patients (18%) with BMS implantation (Figure 2). Baseline characteristics, stratified by stent use, are shown in Table 1. No differences were documented in terms of door-to-balloon time (DES vs. BMS: 67 minutes [interquartile range, IQR 25 to 153] vs. 65 minutes [interquartile range, IQR 25 to 135], p=0.22) and the pre-hospital delay (DES vs. BMS: 195 minutes [interquartile range, IQR 105 to 490] vs. 180 minutes [interquartile range, IQR 99 to 450], p=0.082). In general, rates of BMS implantation were greater among sicker patients with the history of out-of-hospital reanimation, Killip class III/IV, cerebrovascular disease, renal disease, cancer, and Charlson weighted Index ≥2. The DES was more likely used in patients with LM stenosis and MVD. In addition, immediate drug therapy with acetylosalicylic acid, glycoprotein IIb/IIIa inhibitors, beta-blockers and ACE inhibitors/AT antagonists, and statins were more prevalent in patients treated with BMS. In contrast, vasopressors were more frequently used among patients receiving DES as compared to BMS No difference was notified in terms of P2Y12 blockers use between both groups (Table 2).

In-hospital outcomes and predictors of mortality

Overall, in-hospital mortality after DES implantation was lower when compared with BMS (2.6% vs. 7.1%, p<0.001) as well as MACCE (3.5% vs. 7.6%, p<0.001, Table 3).
After adjusting for all different covariables the DES remained a positive independent predictor of survival (OR, 0.51;95%CI, 0.40 to 0.67; p<0.001, see Table 4). In multivariable regression, STEMI, multivessel disease, left main lesion, age, Charlson weighted Index ≥2, out-of-hospital cardiac arrest and Killip III/IV were also identified as predictors of in-hospital mortality (Table 4). No differences were notified in the rate of reinfarction and cerebrovascular events (Table 3). The additional analysis regarding the cardiogenic shock after the pPCI and bleeding rate did not show any differences between both groups receiving DES and BMS (Table 3).

Propensity score matching (2137 DES vs. 2137 BMS)

Also after propensity score matching, the significant reduction in mortality rate and overall MACCE were notified in patients receiving DES as compared to BMS (3.8% vs. 5.8%, p=0.004; 4.8% vs. 6.4%, p=0.033, respectively). DES implantation remained independently associated with reduced risk of in-hospital mortality (aOR, 0.54; 95% CI, 0.39 to 0.76; p<0.001).

Discussion

Our results suggest that DES is beneficial as compared to BMS regarding in-hospital mortality and overall MACCE. This observational analysis includes a real-world population and therefore reflects routine clinical practice.

DES have been proven more effective than BMS to prevent the need for repeat revascularization[13-15]. The restenosis rate of nearly 20 to 30% within 6 to 9 months after BMS implantation has often been called the Achilles' heel of pPCI[16]. The introduction of DES correlated with reduced angiographic restenosis and ischaemia-driven target vessel revascularization (TVR) rates and substantially strengthened the efforts to improve the success rate over the last decades[17, 18]. Restenosis remains the healing response to wire-, balloon- and stent-induced injury and comprising neointimal hyperplasia and vessel remodeling. However the reduction of restenosis rate relates rather to mid-term follow-up, the immediate release of drugs (80-90% eluted within 30 days) can rapidly reduce late loss by targeting cell cycle division also early after stent implantation[19]. However, despite the

reduction in reintervention rates, no robust clinically relevant differences up to 5-year follow-up were convincingly identified[16]. The results abstracted from RCTs revealed no significant differences as regards long-term rates of death or myocardial infarction after DES or BMS use for both off-label and on-label indications[17, 20, 21]. However, the RCTs were primarily limited by population-size. Only the observational studies, with greater numbers of patients presented DES use as a more optimal treatment strategy as compared to BMS associated with reduced death and myocardial infarction[20]. Importantly, the recently published RCTs suggest that the new-generation DES may provide superior clinical outcomes to first-generation DES in patients with coronary artery disease and in real-world practice[22, 23]. The differences were driven in part by the in-hospital MI and early in-stent thrombosis[24].

A major matter of debate is DES implantation during the pPCI in patients with AMI[16]. Our analysis based on unselected AMI subset and reflecting the real-world population documented the improved adverse outcome measure and all-cause death with similar rate of reinfarction. Some prior studies have been similarly in favour of DES (i.e. TYPHOON, HORIZONS-AMI, PASEO, and ZEST-AMI), whereas others presented opposite results[7, 16, 25, 26]. In the PASEO study, sirolimus- and paclitaxel-eluting stents were documented safe and effective as compared to BMS with similar overall mortality[27]. Mauri et al. in their propensity-score-matched group documented, that risk-adjusted mortality rates and repeat revascularization were lower for DES than for BMS among all patients with AMI including both STEMI and NSTEMI, STEMI alone and NSTEMI alone[28]. The reinfarction was reduced after DES implantation as compared to BMS in NSTEMI subset[28]. On the other hand, the PASSION trial have not reveal any benefit after DES implantation as compared to BMS in terms of clinical outcomes after one- and five-year observation[29, 30]. Kaltoft at al. reported 12 deaths before discharge and four classified as probable stent thrombosis in patients implanted with DES and four deaths after BMS implantation including only one possible in-stent thrombosis[7]. The early and late in-stent thrombosis could be caused by i.e. local allergic reactions, inflammation, and delayed endothelialization of the first-generation DES[31]. Meanwhile, newly-engineered DES have been developed with the thinner-strut platforms made of improved alloys providing increased radial strength and radiopacity[5]. This may result in less vascular injury and therefore reduced restenosis and throbogenicity[5, 32]. The EXAMINATION trial comparing everlimus-eluting stents (EES) with BMS in the group of STEMI did not reveal any patient-oriented benefit of EES use[33] being beneficial as regards the risk of restenosis and in-stent thrombosis[33]. The recently published COMFORTABLE trial presented that the newly-designed biodegradable polymer biolimus-eluting stents (BES)

reduce adverse outcomes as compared to BMS mostly due to a significant reduction in rates of reinfarction and reintervention[34]. Also fewer cases of definite in-stent thrombosis were observed in the group of BES when compared with BMS, however the difference was not significant[34]. The use of biodegradable polymers in newly-engineered DES offers the early protection against in-stent thrombosis avoiding its very late proinflammatory and prothrombotic effect[32, 35]. Therefore, concerns regarding the late safety issue with DES are rather related to early-designed DES[8, 36]. New DES replaced the early-generation DES in clinical practice, and what more, the old-fashioned sirolimus-eluting stents, i.e. CYPHER are no longer manufactured[5]. Nowadays, use of DES in AMI has a class IIA recommendation if patients are able to comply with a prolonged regimen of dual antiplatelet therapy[16].

Limitations

The major limitation of the presented study is its observational nature with potential for selection bias and residual confounding. Thus, patients with AMI who receive DES may be less ill than those who receive BMS; our analysis attempted to adjust for these differences to the extent that was possible. Second, the study was underpowered to reveal late in-stent thrombosis which remains the major limitation of early-generation DES. Third, the use of stent type was at the discretion of the operator and no data regarding the use of thrombectomy are available. The number of stents was not systematically recorded and therefore an additional analysis of cases with mixed stents was not possible. Moreover, our database did not allow us to distinguish the particular stent type implanted; therefore, other aspects of the stent design (strut size and thickness, stent material, drug or polymer) and its influence on outcome remains unknown. The present analysis addresses, however, all consecutive patients referred for urgent pPCI due to ACS and reflects the real-world practice. Moreover, since our patients were not randomly assigned, we performed a propensity score matching, to limit the potential biases.

Conclusions

The use of DES in patients with AMI undergoing pPCI appears to be associated with improved mortality and overall in-hospital adverse outcomes as compared to BMS. The promising results of the present analysis bear discussion and therefore call for the extended follow-up and perhaps larger randomized controlled trials to examine this strategy in real-world populations.

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Table 1. Baseline characteristics of AMI patients, who underwent primary PCI according to type of stents {n/N (%)}

Variables	**BMS**	**DES**	**P value**
Number of patients	**2260**	**10094**	
Gender, male (%)	1716/2260 (75.9)	7857/10094 (77.8)	0.051
Age in years, mean (SD)	65.0 (13.2)	62.3 (12.1)	<0.001
Pre-hospital delay (min, median; IQR)	180min (99, 450)	195min (105, 490)	0.082
Resuscitation prior admission	220/2259 (9.7)	572/10094 (5.7)	<0.001
Killip classes 3/4	239/2235 (10.7)	550/10058 (5.5)	<0.001
STEMI	1736/2260 (76.8)	7155/10094 (70.9)	<0.001
Family history	537/1796 (29.9)	3081/8730 (35.3)	<0.001
Current smoker	810/1857 (43.6)	3861/8481 (45.5)	0.14
Dyslipidemia	983/1929 (51.0)	4644/8921 (52.1)	0.39
Hypertension	1179/2084 (56.6)	5280/9511 (55.5)	0.38
Obesity (BMI>30)	366/1808 (20.2)	1697/7995 (21.1)	0.37
Diabetes	328/2104 (15.6)	1570/9650 (16.3)	0.45
Coronary artery disease	525/2205 (23.8)	2883/9968 (28.9)	<0.001
Past history of AMI	202/2166 (9.3)	1260/9862 (12.8)	<0.001
Heart failure	34/2164 (1.6)	149/9856 (1.5)	0.85
Cerebrovascular disease	105/2164 (4.9)	309/9856 (3.1)	<0.001
Renal disease (moderate to severe)	102/2164 (4.7)	338/9856 (3.4)	0.005
Cancer diseases	127/2164 (5.9)	387/9856 (3.9)	<0.001
Charlson Score ≥2	337/2164 (17.4)	1438/9856 (14.6)	0.001
Left main	67/2253 (3.0)	479/10055 (4.8)	<0.001
Multivessel disease	1235/2255 (54.8)	5921/10057 (58.9)	<0.001
Door-to-balloon time (min, median; IQR)	65min (25, 135)	67min (25, 153)	0.22

Data are presented as n (%) or mean±SD or median with inter-quartile range;

AMI=acute myocardial infarction; BMI=body mass index; BMS=bare-metal stent; DES=drug-eluting stent; IQR= inter-quartile range; STEMI=ST-segment elevation myocardial infarction;

Table 2. Immediate drug therapy {n/N (%)}

Variables	**BMS**	**DES**	**P value**
Number of patients	**2260**	**10094**	
ASS	2191/2253 (97.2)	9899/10074 (98.3)	0.002
P2Y12 blocker*	2151/2251 (95.6)	9638/10067 (95.7)	0.69

GP IIb/IIIa	696/2204 (31.6)	3437/9947 (34.6)	0.008
Vasopressors	321/2201 (14.6)	828/9905 (8.4)	0.001
Beta blocker	1176/2218 (53.0)	6385/10003 (63.8)	0.001
ACEI/AT	1177/2221 (53.0)	6089/10021 (60.8)	<0.001
Statin	1700/2232 (76.2)	8264/10028 (82.4)	<0.001

Data are presented as n (%); ASS= acetylosalicylic acid; ACEI= angiotensin-converting-enzyme inhibitor; AT= angiotensin II receptor antagonists; BMS=bare-metal stent; DES=drug-eluting stent; *clopidogrel, or prasugrel or ticagrelor;

Table 3. In-hospital complications and outcome of AMI, who underwent primary PCI according to type of stents {n/N (%)}

	BMS	**DES**	**P value**
Number of patients	**2260**	**10094**	
Complication			
Cardiogenic shock	110/2260 (4.9)	280/10063 (2.8)	<0.001
Cerebrovasular events	9/2260 (0.4)	54/10063 (0.5)	0.51
Bleeding	81/2260 (3.6)	311/10063 (3.1)	0.23
Re-infarction	13/2260 (0.6)	79/10063 (0.8)	0.34
Mortality	160/2260 (7.1)	263/10094 (2.6)	<0.001
MACE*	165/2157 (7.6)	321/9232 (3.5)	<0.001

Data are presented as n (%); BMS=bare-metal stent; DES=drug-eluting stent; *MACE=major adverse cardiac and cerebrovascular event

Table 4. Independent predictor of in-hospital mortality

Variables	**OR**	**95%CI**	**P value**
DES vs. BMS	0.52	0.40–0.68	<0.001
STEMI	1.43	1.06-1.91	0.018
Multivessel disease	1.39	1.06-1.81	0.017
Left main	1.89	1.27-2.81	0.002
Female gender	1.00	0.75-1.32	0.99
Age (per additional year)	1.05	1.04-1.06	<0.001
Charlson weighted Index =>2	2.23	1.71-2.92	<0.001
Resuscitation prior admission	5.91	4.37-7.99	<0.001
Killip class >2	11.6	8.84-15.1	<0.001

BMS=bare-metal stent; DES=drug-eluting stent; OR=odds ratio; STEMI=ST-segment elevation myocardial infarction;

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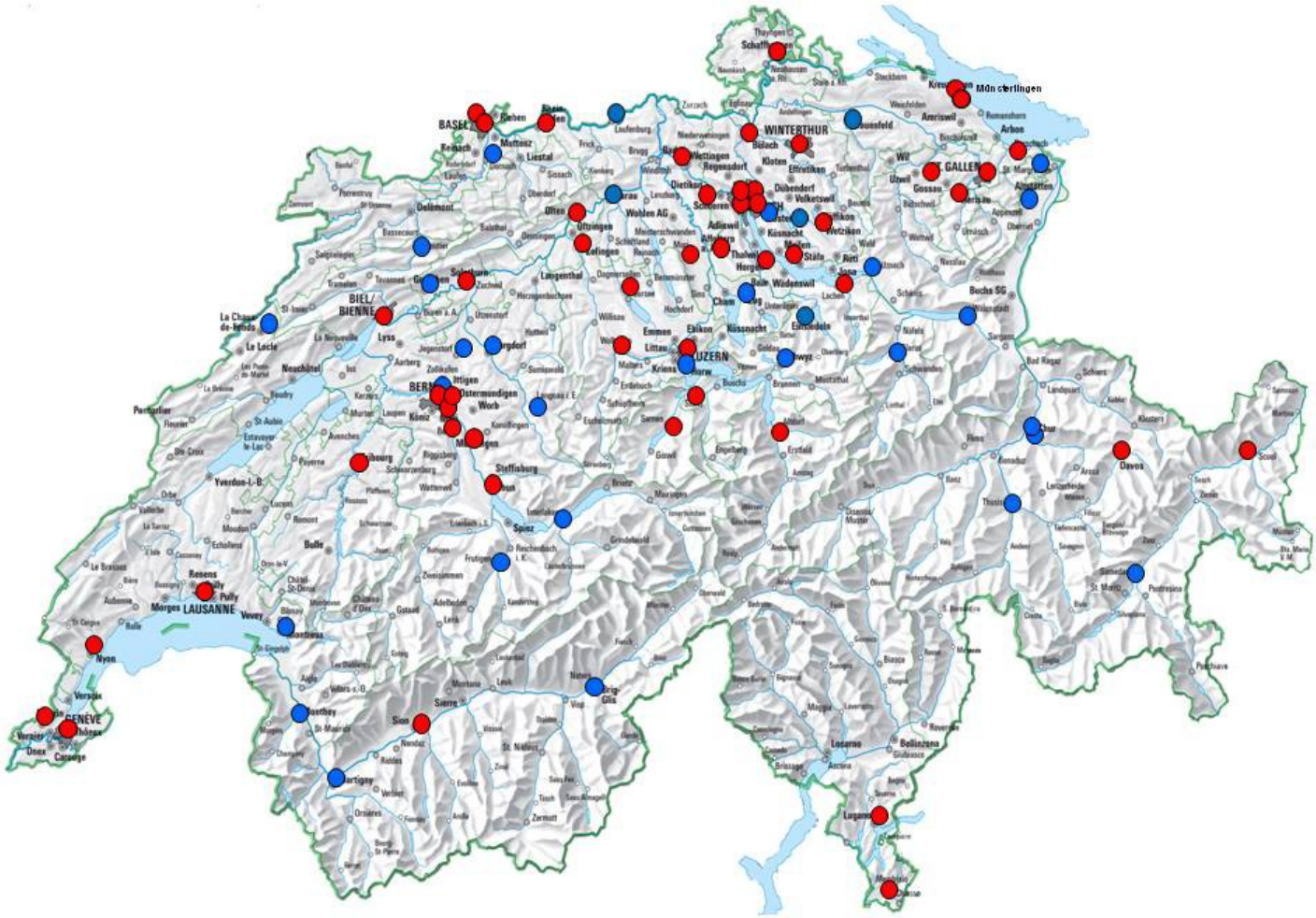
Figure 1. All hospitals who have participated in AMIS project (red color - current participating hospitals)

Figure 2. Study flow chart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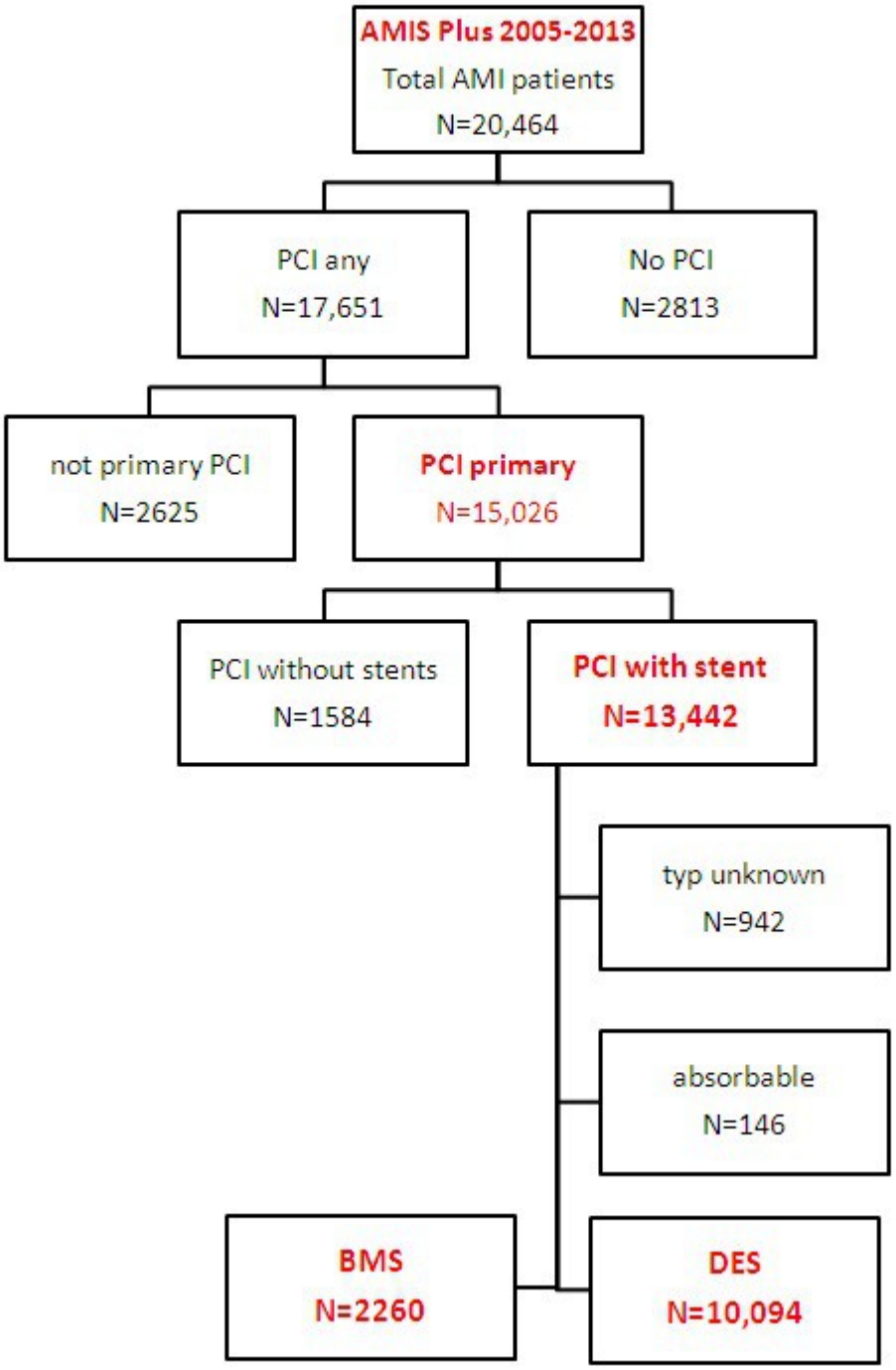
AMIS Plus 2005-2013
Total AMI patients
N=20,464
PCI any
N=17,651
No PCI
N=2813
not primary PCI
N=2625
PCI primary
N=15,026
PCI without stents
N=1584
PCI with stent
N=13,442
typ unknown
N=942
absorbable
N=146
BMS
N=2260
DES
N=10,094